INTERVIEW

Clinical perspectives: Primary ovarian insufficiency

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Dr Nelson has received board certification from the American Board of Obstetrics and Gynecology for specialization in Reproductive Endocrinology. In addition to earning his MD, he holds an MBA from George Mason University in Virginia, where he focussed his studies on human resource management and the management of nonprofit organizations. After several years of private practice, he returned to academia to complete a clinical research attachment at Hammersmith Hospital in London, a fellowship in reproductive endocrinology at George Washington University and a research fellowship at the NIH.

Q: A potentially life-altering condition, how do you help your patients cope with primary ovarian insufficiency? Do you think that its prevalence is increasing?

A: Primary ovarian insufficiency (POI) is indeed a life-altering condition, with many patients considering the diagnosis as a threat to their identity as a woman. Additionally, the disorder is much more than infertility, involving emotional health, physical health, and spiritual wellness. Our research team takes an integrated approach to this situation. We have learned that we need to know the patient at a personal level in order to care for them appropriately. Before we evaluate them, all of our patients answer a series of questions in writing about themselves and how POI has affected their lives.

I share these writings, called 'The Patient Narrative' in confidence with our team. This practice has changed our team dynamics and given greater meaning to our work. The occupational therapy assessment of these women has become a central component of the evaluation, with experts helping people redesign their life in the face of life-altering diagnoses. Our published evidence supports the view that those women who find new meaning and purpose in life, in relation to the diagnosis, seem to do the best.

I am not aware of any published evidence that indicates an increase in the prevalence of overt POI; however, as more women delay childbearing into their 30s, the impact of this disorder on society certainly has increased.

Q: As a continuum of disorders with several different terminologies, which term would aptly describe the condition in your opinion, and why?

A: In my view, Fuller Albright had it right in 1942 when he first named this condition primary ovarian insufficiency. The symptoms may be the same as those seen in women with menopause, but the pathophysiology differs dramatically as menopause results from a depletion of functional primordial follicles.

The other commonly used terms such as, 'premature menopause' and 'premature ovarian failure' are scientifically inaccurate because most women with this condition still have potentially functional follicles remaining in the ovary (about 75% in our most recent publication). Several reports have validated these early findings. Furthermore, the terms menopause and premature ovarian failure are stigmatizing.

In a survey, we found that majority of our patients prefer POI to the other terms. The word 'primary' refers to the fact that the ovary is the primary

problem and 'insufficiency' implies that the condition is a continuum of impaired ovarian function, including diminished ovarian reserve and low responders. Ovarian insufficiency can be occult because the menstrual cycles are still regular, and in such cases, we prefer to use the term 'occult primary ovarian insufficiency.' An elevated basal FSH or a low response to gonadotropin stimulation is required to identify women with occult POI.

Q: What are the tests conducted or the criteria to confirm the disease? Are there any specific guidelines followed in clinical practice?

A: To make the diagnosis of overt POI, one has to take oligo/amenorrhea seriously as a marker of something amiss. Girls who have not had their first menses by age 15 and women below 40 years having more than 90 days between menses need evaluation. It is important to first rule out pregnancy, and then measure FSH and prolactin. If FSH is in the menopausal range, the test needs to be repeated a month later. Two FSH levels in the menopausal range, combined with 4 months of irregular menses, makes the diagnosis of overt POI. To determine the mechanism, the following tests can be performed after appropriately informing the patient of the implications of the tests and obtaining their consent:

- Karyotyping that counts 30 cells, for identifying women with Turner syndrome
- Adrenal antibodies measurement, for detecting women with steroidogenic cell autoimmunity (autoimmune oophoritis)
- *FMR1* gene assessment for the number of CGG repeats, to identify women with *FMR1* premutation

Q: Several studies have noted the association between POI and *FMR1* gene premutation. Considering this, are genetic tests done routinely? What are the implications of the carrier status on patient's health?

A: There is consensus that all women with POI should be offered testing for the *FMR1* gene premutation. Women with the premutation are at risk of having a child with fragile X syndrome, if they are among the 5%-10% of women who get pregnant after the diagnosis of POI. This syndrome is the most common form of heritable mental retardation. The discovery of carrier status has significant implications for other family members with regard to having children with mental retardation. There are also reports that patients who carry the premutation are at risk of developing a neurodegenerative disorder in later life, referred to as fragile X-associated tremor ataxia syndrome (FXTAS). This is more common in men than women.

Q: What are the different therapeutic strategies for POI? In your experience, which is the most useful method?

A: As noted above, women with POI need an integrated approach to their care (as a team approach works best), covering issues related to physical health, emotional health, and meaning in life.

Q: Since the long-term safety of hormone replacement therapy is not clearly known, would you still recommend it to all your patients? Are there alternative treatment strategies that you prefer to customize for your patients?

A: By definition, women with POI are less than 40 years old. They are not menopausal women who are young, but are young women who are missing the ovarian hormones that their peers have normally. For such women, it truly is hormone replacement. My first line recommendation is that women with POI do best by replacing the estradiol they are missing through a transdermal or transvaginal delivery of 100 micrograms per day of estradiol. The 100 microgram dose is a full replacement dose of estradiol for young women. These routes of administration avoid the first pass effect on the liver that takes place with oral estrogens. This first pass effect significantly increases the risk of thromboembolic phenomena.

Patients need to take a full replacement dose of progestin to reduce the risk of endometrial hyperplasia and endometrial cancer. Available data supports the use of medroxyprogesterone acetate as a first line therapy in a dose of 10 mg/day, for the first 12 days of each month. Patients should keep a menstrual calendar and get a pregnancy test if they fail to menstruate when expected. I recommend that women with POI take this regimen until age 50, which is the average age of menopause.

There is limited evidence on other regimens in this population, and I have little confidence in alternative strategies with regard to hormone replacement in this population.

Q: Infertility is common in POI patients, having no proven therapeutic strategy for restoring ovarian function. In your experience, what are the interventions that have the likelihood of increasing the chances of conception? Would you say spontaneous conception is possible in such patients?

A: There are no proven strategies for increasing the chances of conception by improving ovarian function. It is important to inform patients with POI that there is a

5%-10% chance of spontaneous conception despite the diagnosis. If they are interested in pregnancy, they should do what it takes to assure that there will be sperm waiting for the egg that might ovulate now and then. Sperm can live in a woman's genital system for 3 to 4 days, so intercourse 2 or 3 times a week meets this objective. Our serial hormonal testing suggests that about 20% of women with POI will ovulate over four months of weekly sampling.

Women with spontaneous 46 XX POI have intermittent and unpredictable ovarian function that can continue for decades. There is one report in literature of a woman developing POI at age 27 and having a normal delivery at age 44.

The emotional shock of the diagnosis can be quite severe and most women need to process the associated grief, which takes time. We know that the grief of losing a loved one takes about three years to get to the resolution phase. Many women tell me that getting this diagnosis was like losing a loved one, losing the children they hoped to have in the usual manner. It also takes time for the husband and wife to get on the same page with regard to next steps. I suggest that couples should consider permitting some time for natural conception while they process the grief. This needs to be individualized, but in view of the level of grief I have seen in these women, I suggest considering a processing period of three years before moving forward. Obviously, this is not a hard and fast rule, just a place to start considering how to move forward.

Q: Do you recommend ART to all patients, since several studies have demonstrated that oocyte donation is the best strategy to achieve pregnancy in women with POI? What are the advantages and limitations of this strategy?

A: The first question is whether they want to be a parent or not. Some women tell me they never got 'the motherhood gene' and never wanted to have children. Oocyte donation obviously is not for them. The next question is whether the couple is interested in high-tech approaches. Some couples have financial or ethical concerns; oocyte donation is not for them. For such couples, the options include adoption, foster children, or deciding to live child free. For couples who have the means and the desire to adopt high-tech approaches, oocyte donation works extremely well. There is some evidence to suggest a higher incidence of pregnancy complications for this method, and a minimal increase in the rate of birth malformations. However, for most couples these risks are not of great enough magnitude to decide against the approach. Embryo donation is another high-tech approach that can work well and cost less.

Q: With the lack of sufficient evidence on several aspects of POI, would you like to see more studies being done in any specific area?

A: Absolutely! This is a rare condition made up of a host of ultra rare diseases. To make substantial research progress, we need to develop an international consortium with a registry that will provide insights into the natural history of this disorder and a base for controlled trials. ■

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